# Paraquat Intoxication – experience of an Internal Medicine ward for 18 years

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## Abstract

Introduction: Paraquat is a contact herbicide commercially available since 1962. Paraquat intoxication (PI) is usually voluntary and highly lethal, since there is no effective antidote. Toxicity occurs through cyclic redox reactions, damaging mainly the kidneys and lungs.

Aim, material and methods: featuring the clinical presentation, management and outcome of patients with PI over an 18 years period (from the 01st January 1993 to the 31st December 2010) through the retrospective analysis of clinical files and comparing the survivors and the deceased.

Results: Thirty-one cases of Paraquat intoxication were included, with a male: female ratio 1:1. Age range from 13 to 80 years, mean age 42.4years (±18.7).All intoxications were voluntary and by oral route. There was statistical difference in the amount ingested (22.1 mL vs. 72.7 mL, p<0.0005). A non-significant trend to a longer delay until getting medical attention in the deceased group (1.6 h vs. 3.2 h, p=0.091). Statistical significance was found between mortality and leukocytosis, hypocapnea, hypoxemia, LDH, alkaline phosphatase and AST. There was no difference between groups according to treatment options, although hemocarboperfusion was used more often in the deceased group (53.9% vs. 66.7%, p=0.471) and corticosteroids in the survivor group (61.5% *vs.* 44.4%, p=0.350). Mortality rate was 58.1% (66.7% in the first 72 hours), due to respiratory insufficiency and multiple organ failure. Variable levels of pulmonary fibrosis occurred in 38.5% of the survivors.

Discussion & Conclusion: Paraquat intoxication has a poor prognosis with limited efficiency of treatment approaches. The relation between Paraquat in the urine and the time elapsed after ingestion is the main determinant factor in the prognosis. In this study the presence of dyspnea, hypocapnea and hypoxemia was linked to a bad prognosis. There was no statistical difference between the available treatment options.


Key words: Paraquat, Intoxication, hemocarboperfusion, cyclophosphamide, Herbicide, Gramoxone®.

## INTRODUCTION

Paraquat (PQ), 1,1'-dimethyl-4,4'-bipyridinium dichloride, is a widely used contact herbicide, given its efficacy and low price, as well as its environmental safety and stability. Created in 1882, its use as an herbicide was only discovered in 1955, and it was marketed for the first time in 1962.[1] The first fatal cases of PQ poisoning occurred in 1964 and were reported in 1966.[2] In spite of its high toxicity, it is available in nearly one hundred countries. In Portugal, it was marketed under the trade name Gramoxone®. On the 30th July 2007, the Directorate-General for Agriculture and Rural Development issued a circular banning the sale of products with PQ. However, it is still possible to buy PQ in many places.[3]

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Occupational exposure to PQ does not pose a health risk if the safety rules are followed.[6] However, it is potentially fatal if ingested. Absorption occurs in the small intestine and reaches peak plasma concentration between two and four hours after ingestion. Accumulation occurs mainly in the lungs.[1]

The toxicity of PQ results in multiple oxidation--reduction, or redox reactions, with the formation of oxygen free radicals. The severity of intoxication is correlated with the quantity ingested. Poisoning at doses lower than 20mg/kg is usually asymptomatic, or may only present gastrointestinal effects, and complete recovery is possible. Moderate poisoning (20 to 40 mg/kg) initially causes damage to the mucous membranes through corrosive action, kidney failure from acute tubular necrosis, and liver dysfunction. Subsequently, lung lesions lead to progressive pulmonary fibrosis, and death within two to four weeks. Ingestion of doses higher than 40 mg/kg causes severe poisoning, with death from multiple organ failure within the first 24 to 48 hours.1

The prognosis of PQ intoxication is determined by

**TABLE I**

**Clinical manifestations on admission**

| | Total (n=31) | Survivors (n=13) | Deceased (n=18) | *p* |
|---|---|---|---|---|
| Odynophagia | 28 (90,32%) | 11 (84,62%) | 17 (94,44%) | 0,836 |
| Burns | 25 (80,65%) | 9 (69,23%) | 16 (88,89%) | 0,187 |
| Dyspnea | **17 (54,84%)** | **4 (30,77%)** | **13 (72,22%)** | **0,027** |
| Oligoanuria | **14 (45,16%)** | **3 (23,08%)** | **11 (61,11%)** | **0,043** |
| Fever | 10 (32,26%) | 4 (30,77%) | 6 (33,33%) | 0,880 |
| Nauseas / vomiting | 8 (25,81%) | 2 (15,38%) | 6 (33,33%) | 0,270 |
| Abdominal pain | 7 (22,58%) | 2 (15,38%) | 5 (27,78%) | 0,421 |
| Diarrhea | 4 (12,90%) | 1 (7,69%) | 3 (16,67%) | 0,472 |

The rows highlighted in gray represent significant statistical correlation.

plasma concentrations, using logarithmic regression curves and the Severity Index of PQ Poisoning. Rapid diagnosis can be made through urine testing for Paraquat (sodium dithionite test), a semi-quantitative detection method with a sensitivity threshold of 1 µg/mL.[1]

Treatment consists of several different approaches: 1) prevention of absorption through gastric lavage and the use of adsorbents such as activated charcoal or Fuller's Earth, 2) promotion of elimination by forced diuresis or extracorporeal elimination methods, like hemodialysis or hemocarboperfusion,[1,4] 3) modulation of the inflammatory process, with the administration of deferoxamine, n-acetylcysteine, pulse corticosteroid therapy, and cyclophosphamide.[1,5,6] Supporting medical therapy consists of hydration, analgesia, and hemodynamic support. The administration of oxygen is contraindicated because it increases the toxicity of PQ.[1]

## OBJECTIVES

Characterization of the clinical presentation, treatment, and evolution of patients with PQ intoxication. Comparison of the groups of surviving and deceased patients, seeking to establish prognostic indicators.

## MATERIAL AND METHODS

Retrospective analysis of the cases of PQ intoxication admitted to the Internal Medicine Service of Coimbra University Hospitals between 01/01/1993 and 31/12/2010. Cases of documented ingestion and/or positive urine testing for Paraquat were included. Data collected included demographics, amount ingested and time elapsed before medical observation, clinical manifestations, changes in laboratory test results, treatment, evolution, and mortality. Comparison between surviving and deceased patients using descriptive statistics and hypothesis testing (Student's t--test and odds ratio, 95%).

## RESULTS

During the period of this study, thirty-one patients with PQ poisoning were admitted to this Service, five of them after marketing of PQ had been suspended, reflecting an incidence practically equal to that in the years prior to the ban. There was no gender predominance, either in absolute terms, or in the survivor and deceased subgroups. Patient ages ranged from thirteen to eighty years. The average age of the survivors was significantly lower than that of the patients who died (33.62 vs. 48.47 years of age, p=0.023).

All the poisonings were oral and voluntary. The amount of PQ ingested was difficult to determine, being based on the accounts of the patients and on the information collected by the medical team on site. In six cases (five deaths) it was not possible to determine the amount ingested. The approximate amount ingested by the survivors was significantly less (22.08 mL vs. 76.69 mL, p<0.0005). As regards the time elapsed between ingestion and initial medical attention, there was a tendency towards a shorter period among the survivors (1.6 h vs. 3.2 h, p=0.091). Paraquat traces in the blood cannot be determined at this Hospital. Urine tests for Paraquat were positive in all cases.

The most common clinical manifestations were odynophagia in 90.32% of the patients, burns of the oropharynx in 80.65%, dyspnea in 54.84%, and oligo-anuria in 45.16%. Dyspnea (72.22% vs. 30.77%, p=0.027) and oligo-anuria (61.11% vs. 23.08%, p=0.043) were significantly more common among the patients who died *(Table 1)*.

Complementary exams performed on admission detected signs of respiratory failure (pO2 < 80 mmHg) in 64.52% of patients, kidney failure (creatinine > 1.3

**TABLE II**

**Laboratory values on admission**

| | Survivors (n=13) | Deceased (n=18) | *p* |
|---|---|---|---|
| Leukocytes (G/L) | 11,3 (±4,67) | 14,72 (±3,85) | 0,033 |
| Hemoglobin (g/dL) | 13,83 (±1,24) | 13,44 (±1,25) | 0,397 |
| pO2 (mmHg) | 82,87 (±12,92) | 68,98 (±14,83) | 0,011 |
| pCO2 (mmHg) | 38,12 (±3,3) | 32,46 (±4,78) | 0,001 |
| Creatinine (mg/dL) | 1,56 (±1,76) | 2,3 (±1,59) | 0,231 |
| LDH (U/L) | 366 (±186,73) | 595,89 (±301,07) | 0,022 |
| GOT (U/L) | 37,31 (±21,49) | 82,61 (±72,24) | 0,021 |
| GTP (U/L) | 25,92 (±7,9) | 55,89 (±66,88) | 0,077 |
| Total bilirubin (mg/dL) | 0,68 (±0,24) | 0,91 (±0,54) | 0,163 |
| CK (U/L) | 94,23 (±39,34) | 134,74 (±64,36) | 0,054 |
| GGT (U/L) | 31,46 (±22,78) | 64,83 (±69,71) | 0,072 |
| Alkaline phosphatase (U/L) | 57,08 (±11,82) | 68,61 (±15,59) | 0,033 |

Mean values ± standard deviation, confidence interval 95%.
The rows highlighted in gray represent significant statistical correlation.
pO2 – partial pressure of oxygen; pCO2 – partial pressure of carbon dioxide; LDH – lactate dehydrogenase;
GOT – Glutamate oxaloacetate transaminase; GPT – Glutamate pyruvate transaminase; CK – Creatinine kinase; GGT - gamma glutamyl transpeptidase.

mg/dL) in 45.16% of the patients, and liver failure (INR > 1.5) in 38.71%. Hemogram leukocyte counts were significantly higher in the group of deceased patients (11.30 G/L vs. 14.72 G/L, P=0.033), while hemoglobin levels showed no differences. Biochemistry showed significant differences in LDH (366.00 U/L vs. 595.89 U/L, P=0.022), GOT (37.31 U/L vs. 82.61 U/L, p=0.021), and alkaline phosphatase (57.08 U/L vs. 68.61 U/L, P=0.033). GPT, GGT, total bilirubin, and serum creatinine all tended to have higher values in the patients who died. In relation to gasometrical parameters on admission, hypoxemia (82.87mmHg vs. 68.98mmHg, p=0.011) and hypocapnea (38.12mmHg vs. 32.46 mmHg, p=0.001) were significantly more common in the deceased patients *(Table II)*.

There were no significant differences between treatment regimens followed. Gastric lavage (96.77%) and activated charcoal (87.10%) were the most frequently used. Hemocarboperfusion was performed in 61.29% of cases (nineteen patients), with a tendency towards higher usage among the patients who died (53.85% vs. 66.67%, p=0.471). Corticosteroids were administered in 51.61% of cases, predominantly among the survivors (61.54% vs. 44.44%, p=0.350). A protocol of cyclophosphamide 15mg/Kg/day (2 days) and methylprednisolone 1gr/day (3 days) was tried on thirteen patients (41.94%), with no benefit identified for either reduced mortality or for the prevention of pulmonary fibrosis, since eight patients died and, of the five survivors, two developed fibrosis *(Table III)*.

There were eighteen deaths (58.06%), two thirds of them within the first seventy-two hours, due to respiratory and multiple organ failure. The others died from multiple organ failure within a three-week period. The thirteen survivors were followed-up as outpatients by the Internal Medicine Service for an average of sixteen months (± 9.57 months). Varying levels of pulmonary fibrosis were detected in five patients (38.46%).

## DISCUSSION

Despite the suspension of marketing of PQ in Portugal in July 2007, its subsequent sale was possible in various parts of the country,[3,9] which explains the occurrence of five cases of poisoning following the ban.

The results of this series are similar to those of other studies published in this journal in 1996[7] and 2001,[8] also conducted at Coimbra University Hospitals. The data in the present series are not intended as an update of the previously published series. In this case series, the mortality rate was 58.06%, which coincides with the data published in the national series (50.00%,[7] 51.40%,[8] and 63.00%[4]). However, the mortality rate was lower than in most of the international series.[10,11] Because the present results include only patients admitted to the Internal Medicine Service, the mortality rate may have been higher if both patients admitted to the Intensive Care Service and those who died while in the Emergency Service were included, explaining the difference found. In this study, the average age of the deceased patients was significantly higher than that of the survivors, a result inconsistent with the data published in other national series.[7,8] Mortality depends, above all, on the quantity ingested and on the PQ blood tests, which are not related to the patient's age. Analyzing the dif-

**TABLE III**

**Treatment regimens followed**

| | Total (n=31) | Survivors (n=13) | Deceased (n=18) | *p* |
|---|---|---|---|---|
| Gastric lavage | 30 (96,77%) | 13 (100,00%) | 17 (94,44%) | n.d. |
| Activated charcoal | 27 (87,10%) | 11 (84,62%) | 16 (88,89%) | 0,727 |
| Hemocarboperfusion | 19 (61,29%) | 7 (53,85%) | 12 (66,67%) | 0,471 |
| Corticosteroids* | 16 (51,61%) | 8 (61,54%) | 8 (44,44%) | 0,350 |
| Methylprednisolone/ Cyclophosphamide | 13 (41,94%) | 5 (38,46%) | 8 (44,44%) | 0,739 |
| Laxatives | 12 (38,71%) | 6 (46,15%) | 6 (33,33%) | 0,471 |
| Fuller's Earth | 7 (22,58%) | 3 (23,08%) | 4 (22,22%) | 0,955 |
| Vitamina C | 6 (19,35%) | 3 (23,08%) | 3 (16,67%) | 0,657 |

*This includes patients who received corticosteroids in the methylprednisolone and cyclophosphamide protocol
nd – not determinable.

ferences between the two groups, a higher prevalence of dyspnea, hypoxemia, and hypocapnea was found in the group of deceased patients, which in clinical practice, is manifested as accumulations of PQ mainly in the lungs, and consequent lesion. There was also a higher prevalence of oligoanuria among the deceased patients, a fact that is relevant because PQ is eliminated mainly by the renal system.[1, 6]

In this case series, the diagnosis of PQ intoxication was made by documented ingestion and/or positive PQ urine test results. PQ blood testing is the best means for the evaluation of poisoning and the determination of the prognosis,[1] but is not performed in this hospital. The amount ingested and the time elapsed from ingestion to the first medical observation are not very reliable. However, there was statistical correlation between the estimated amount ingested and mortality, therefore determination of the amount is crucial.

Although renal elimination of PQ is three to ten times more effective than hemocarboperfusion,[1,6] acute renal failure often arises during the course of intoxication, limiting the amount of PQ eliminated. From this perspective, techniques of extracorporeal elimination, like hemodialysis and especially hemocarboperfusion, have been used, but with questionable efficacy. A Korean study of one hundred and five patients demonstrated the benefits of this dialysis technique.[12] Conflicting results were obtained in a Portuguese study that showed no reduction in mortality rate.[4] However, a retrospective analysis by the authors concluded that most of the patients who died had serum values above the range indicated for the technique. Blood testing for PQ is thus critical for determining the appropriate use of hemocarboperfusion. Prevention of pulmonary fibrosis using protocols involving the administration of pulse corticosteroids and cyclophosphamide has shown beneficial results in several studies.[13,14] In 2010, a publication of the *Cochrane Review* concluded that there is less risk of death in patients who undergo this treatment (relative risk – 0.72).[5] In the present study, there was no proven benefit from the use of hemocarboperfusion or of a protocol of methylprednisolone and cyclophosphamide. A Portuguese study showed the presence of toxic levels in various samples of body tissue collected during autopsies of patients with PQ poisoning,[9] demonstrating the ineffectiveness of available therapies.

The present study aims to illustrate the experience of this Service with PQ poisoning, and to warn of the possibility of its occurrence, despite the marketing ban. Moreover, the development of a possible antidote like sodium salicylate[1,15] could lead to its reintroduction onto the market, given both the economic interest in, and the efficacy of PQ as an herbicide. ■

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